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Anticholinergic burden and risk of stroke and death in people with different types of dementia

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Running title: Anticholinergic burden and stroke and death

Abstract

Background

Anticholinergic burden is associated with poorer cognitive and functional outcomes in people with dementia. However, the impact of anticholinergics on significant adverse outcomes such as stroke has not been studied previously.

Objective

To investigate the association between total anticholinergic cognitive burden (ACB) and risk of stroke and death in people with different dementia subtypes.

Methods

This was a cohort study of 39107 people with dementia and no prior history of stroke registered in the Swedish Dementia Registry (SveDem) from 2008 – 2014. Data were extracted from the Swedish Prescribed Drug Register, the Swedish National Patient Register and the Swedish Total Population Register. Competing risk regression models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between time-varying ACB score and risk of stroke and all-cause mortality.

Results

During a mean follow-up period of 2.31 (standard deviation 1.66) years, 11224 (28.7%) individuals had a stroke or died. Compared with non-users of anticholinergic medications, ACB score of 1 (HR 1.09, 95%CI 1.04 – 1.14) and ACB score of ≥2 (HR 1.20, 95%CI 1.14 – 1.26) increased the risk of developing the composite outcome of stroke and death. When stratifying by

dementia disorder, the association remained significant in Alzheimer's disease, mixed dementia and vascular dementia.

Conclusions

The use of anticholinergic medicines may be associated with an increased risk of stroke and death in people with dementia. A dose-response relationship was observed. Careful consideration should be made when prescribing medications with anticholinergic properties to people with dementia.

Key words

Anticholinergics, stroke, dementia, Alzheimer disease, vascular dementia, cohort studies, registries

Introduction

Medications with anticholinergic properties are commonly used in older people for a range of therapeutic indications. Anticholinergic burden, the cumulative effect of taking multiple medicines with anticholinergic properties, has been found to be associated with significant adverse effects on cognitive and physical function in older people; however, there is limited evidence for mortality and cerebrovascular outcomes.[1-5] A meta-analysis concluded that every unit increase in the anticholinergic cognitive burden (ACB) scale was associated with a doubling in odds of all-cause mortality (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.82 – 2.33).[3] A study in the general older population reported a significant dose-response association between total ACB score and mortality and cardiovascular outcomes, including stroke.[6]

People with dementia have been shown to be high users of medications with anticholinergic properties.[7] Whilst the negative effects of anticholinergic medications on cognition and dementia progression have been studied extensively,[8] few studies have explored the impact of anticholinergics on other important adverse outcomes including stroke and mortality in individuals with dementia. There is some evidence to suggest that there is an increased risk of mortality with the use of anticholinergic medications in people with dementia; however, findings are inconsistent.[9-11] Additionally, these studies are limited by small sample sizes, short durations of follow-up and failure to differentiate between different subtypes of dementia which may be important regarding underlying mechanisms of the disease. To date, the association between anticholinergic burden and stroke risk in people with dementia has not been investigated. This is of importance as people with dementia are at a two-fold greater risk of stroke compared to those without dementia.[12]

The aim of this study was to investigate the association between anticholinergic burden with stroke and death in people with dementia, and whether this association varied by type of dementia disorder.

Methods

Study population

This was a cohort study based on individuals registered at the time of the dementia diagnosis in the Swedish Dementia Registry (SveDem, www.svedem.se) from 2008 to 2014. The Swedish Dementia Registry (SveDem) is a national quality registry for monitoring the diagnosis, treatment and care of people with dementia in Sweden.[13] It covers 100% of memory clinics and 75% of primary care units in Sweden. It included a total of 48766 individuals with newly diagnosed dementia from 2008 to 2014. To be eligible for inclusion in this study, participants needed to have no prior history of stroke and complete baseline data. After excluding those with previous stroke (n=6191, 12.7%) and missing data (n=3468, 7.1%), a total of 39107 people were included in the analyses.

Data sources

Information on dispensed drugs was extracted from the Swedish Prescribed Drug Register. All prescriptions dispensed by Swedish pharmacies are captured in this register together with unique patient identifiers. The National Board of Health and Welfare maintains this register and coverage is >99%.[14] All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) code. To be considered a user of a medication, participants had to have at least 3 prescriptions or 20 unit doses dispensed in the previous year.

Information on medical diagnoses at baseline and during follow-up were extracted from the Swedish National Patient Register. This register contains prospectively collected data from all inpatient and specialized outpatient visits in Sweden and is maintained by the Swedish National Board of Health and Welfare. The coverage of inpatient discharges is >99%.[15] The medical diagnoses of all individuals are classified according to the International Classification of Diseases, Tenth Revision, (ICD-10). Information on all-cause mortality were extracted from the Swedish Total Population Register. This register is maintained by Statistics Sweden and covers 100% of all deaths in Sweden.[16]

Anticholinergic exposure measure

Anticholinergic exposure was defined using the Anticholinergic Cognitive Burden scale (ACB).[17, 18] The ACB scale assigns a score of zero for medications with no known anticholinergic activity, one for medication with possible anticholinergic properties, two for medications with definite clinical anticholinergic properties, and three for medications with definite anticholinergic properties that may cause delirium (Suplementary Table 1). The ACB scale is the most frequently validated tool for assessing the effect of anticholinergic medications on adverse outcomes.[4] A total ACB score was calculated for each patient annually by adding the individual scores of different medications in a patient's prescribed regimen. Annual total ACB score was analyzed as a time-varying variable i.e. the most recent score prior to outcome or study end was used in the analysis. Scores were further categorized into 0, 1 or ≥2.

Outcomes

The primary outcome was the composite of first stroke (any) and all-cause mortality. Secondary outcomes were death, any stroke and ischemic stroke. Stroke was defined as first occurrence of

ICD-10 codes I61, I63 or I64. Ischemic stroke was defined as first occurrence of ICD-10 code I63.

Confounders

Demographic data at baseline were obtained from SveDem and included age, sex, Mini-mental state examination (MMSE),[19] living situation (institutionalized, living alone or living at home with a co-resident), home care use and dementia disorder.[13] Dementia diagnoses were made according to ICD-10 criteria[20] and coded as Alzheimer's disease (AD), vascular dementia, mixed dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease dementia (PDD), unspecified dementia and other dementia types. Charlson comorbidity index was used as a measure of the number and severity of comorbid conditions at baseline.[21] Antidementia drugs at baseline were defined as ATC code N06D.

Statistical analysis

Analysis of variance and chi square statistics were used to compare participant baseline characteristics according to ACB score. Baseline was defined as the date of dementia diagnosis. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association between time-varying annual total ACB score and the primary outcome and all-cause death. Adjusted subdistribution HRs (sHRs) and 95% CIs were calculated for the occurrence of any incident stroke and ischemic stroke, adjusting for mortality as a competing risk. All multivariable models were adjusted for age, sex, Charlson Comorbidity Index, living situation, home care, dementia disorder, MMSE and use of antidementia drugs at baseline. Survival time was defined as the time from date of dementia diagnosis (index date) to date of first stroke, death or 31 December 2014, whichever came first.

Subgroup analyses according to dementia disorder subtype was performed. To explore whether the association between anticholinergic burden and stroke and death was due to long-term effects, we also performed a sensitivity analysis using baseline total ACB score as the exposure i.e. total ACB score calculated based on medication use in the year preceding dementia diagnosis.

Ethical considerations

All patients in SveDem were informed about their participation in the registry and had the right to decline participation or withdraw consent. This study was approved by the regional human ethics committee in Stockholm (approval number 2015/743-31/4). Data were coded and anonymized before statistical analyses.

Results

Study population and characteristics

The study cohort consisted of 39107 people with a mean age of 79.9 (standard deviation [SD], 7.90) years with the majority being female (60.7%). At baseline, 24573 (62.8%) participants had an ACB score of 0, 8239 (21.1%) a score of 1 and 6295 (16.1%) a score of ≥2. The mean ACB score at baseline was 0.67 (range: 0 to 12) and the mean time-varying ACB score was 0.73 (range: 0 to 12). The most commonly used drugs contributing to ACB score ≥1 were metoprolol (C07AB02) (39.6%), furosemide (C03AC01) (25.0%), and warfarin (B01AA03) (13.4%). Participants with higher ACB scores were more likely to be older, institionalized, receive home care, have a greater number of comorbidities, take a higher number of drugs and be less likely to use antidementia drugs. Whilst they were less likely to have AD, those with higher ACB scores were more likely to be diagnosed with other dementia subtypes including mixed dementia, vascular dementia and PDD. Detailed demographic information is reported in Table 1.

Risk of death and stroke in the dementia cohort

During the follow-up period (mean [SD] 2.31 [1.66] years), 11224 (28.7%) individuals had a stroke or died. Crude incidence rates for the primary outcome of the composite of stroke and death were higher in those with higher ACB score (111, 130 and 155/1000 person-years, for ACB scores 0, 1 and ≥2, respectively) (Table 2). The individual crude incidence rates for death, stroke and ischemic stroke similarly increased with increasing ACB scores.

After adjusting for potential confounders, time-varying ACB score was associated with an increased risk of developing the primary outcome (HR 1.05, 95%CI 1.03 – 1.06) (Table 3). When categorizing time-varying ACB score, ACB score of 1 (HR 1.09, 95%CI 1.04 – 1.14) and ACB score of ≥2 (HR 1.20, 95%CI 1.14 – 1.26) were associated with the primary outcome, indicating a dose-response relationship. Similar findings were found for the outcome of death with continuous ACB score (HR 1.04, 95%CI 1.02 – 1.06), and categorized ACB score of 1 (HR 1.09, 95%CI 1.04 – 1.14) and ACB score of ≥2 (HR 1.18, 95%CI 1.12 – 1.24) associated with an increased risk of death. A significant association was found between ACB score and any stroke (sHR 1.11, 95%CI 1.07 – 1.15) and ischemic stroke (sHR 1.06, 95%CI 1.02 – 1.11); however, this remained significant only for higher ACB score (≥2) (any stroke: sHR 1.13, 95%CI 1.00 – 1.27; ischemic stroke: sHR 1.15, 95%CI 1.00 – 1.31). Sensitivity analyses using baseline ACB score produced similar results (Supplementary Table 2).

Table 4 reports the hazard ratios for the association between time-varying ACB scores and the primary outcome, stratified by dementia disorder. Time-varying ACB score was associated with the primary outcome for patients with AD (HR 1.08, 95%CI 1.05 – 1.12), mixed dementia (HR

1.05, 95%CI 1.01 – 1.09), vascular dementia (HR 1.04, 95%CI 1.01 – 1.08) and unspecified dementia (HR 1.06, 95%CI 1.02 – 1.09). When categorizing ACB score, ACB score of ≥2 remained significantly associated with the primary outcome for these dementia disorders. Compared with an ACB score of 0, an ACB score of 1 was found to be associated with a reduced risk of developing the primary outcome in patients with Parkinsons disease dementia (HR 0.53, 95%CI 0.34 – 0.83). Sensitivity analyses found no significant association between baseline ACB score and the primary outcome after stratifying by dementia disorder, except for people with AD or unspecified dementia with ACB score of ≥2 (Supplementary Table 3).

Discussion

Our study found that higher total anticholinergic burden was associated with an increased risk of all-cause mortality and stroke in people with dementia, compared with those with lower or no anticholinergic burden. This association remained significant in those with AD, mixed dementia and vascular dementia after stratifying by dementia disorder.

Previous studies of anticholinergic burden and mortality in people with dementia have shown mixed findings. A recent study by Cross et al. reported that time-dependent ACB scores were associated with mortality (adjusted HR 1.18, 95% CI 1.02 – 1.32) in older people with cognitive impairment attending Australian memory clinics. Another study by Gnijdic et al. reported that baseline anticholinergic burden, measured using the Drug Burden Index (DBI), was associated with one-year mortality (adjusted HR 1.21, 95%CI 1.09 – 1.33) in people with AD in Finland. Conversely, other studies have found no association between the use of medications with anticholinergic properties and mortality in people with dementia.[11, 22]

To date, there has been limited research into the association between anticholinergic burden and stroke risk in people with dementia. However, there is evidence to suggest a possible association between anticholinergics and cardiovascular and cerebrovascular outcomes in the general older population.[23] Higher ACB scores have been found to be associated with both mortality and cardiovascular disease incidence, including stroke.[6, 24] Additionally, higher ACB scores in older patients with cardiovascular disease has been shown to increase risk of hospitalization and mortality.[25, 26]

There are a few potential mechanisms which may explain why anticholinergic medications may increase mortality and incidence of stroke. It has been suggested that anticholinergic medications have pro-arrhythmic and pro-ischaemic properties.[27, 28] Anticholinergics may have an effect on cardiovascular homeostasis, producing tachycardia and orthostatic hypotension, both of which may be associated with an increased risk for ischemic stroke. Additionally, given the cholinergic system has a role in regulating immune response, another potential mechanism may be through immunomodulation. Anticholinergics may inhibit immune system processes leading to inflammatory reponses and an increased risk of stroke and mortality in people with dementia with underlying risk factors.[29]

To our knowledge, no previous studies have investigated the impact of anticholinergic medications across different dementia subtypes. Our study found that the regular use of definite anticholinergics (ACB score of ≥2) was associated with increased risk of stroke and death in those dementia subtypes with a probable underlying vascular component (AD, mixed dementia and vascular dementia). This may indicate these patients are inherently at risk of stroke and early mortality and that the use of anticholinergic medications may compound this. Alternatively,

several cardiovascular medications, such as diuretics, antihypertensives and antithrombotics, have anticholinergic properties, and these drugs were the main contributors to ACB score in our study population. It is thus possible that the use of these medications is reflective of underlying vascular problems that can increase risk of stroke and death in this population.

The use of anticholinergics in people with dementia is questionable, given their negative impact on cognition.[5] The use of anticholinergics in conjuction with antidementia drugs, such as acetylcholinesterase inhibitors, appears counterintuitive given the conflicting mechanisms of actions of the two drug classes.[30] Acetylcholinesterase inhibitors have been shown to be associated with a reduced risk of stroke and mortality in people with Alzheimer's disease and dementia.[31, 32] The use of anticholinergic medications may thus oppose these protective effects. Although partipants in our study were less likely to be using an acetylcholinesterase inhibitor if they had a higher ACB score, 40% of those with an ACB score of ≥2 were still concurrently prescribed an acetylcholinesterase inhibitor.

Our study observed a linear dose-response relationship between anticholinergic burden and risk of mortality and stroke. In particular, we observed that the use of regular medications with definite anticholinergic properties (ACB score of ≥2) were associated with a 20% increase in the risk of stroke or death in people with dementia. This would be the equivalent of an individual taking a minimum of two ACB score 1 drugs e.g. metoprolol and venlafaxine together, or a single ACB score 2 or 3 drug e.g carbamazepine or oxybutynin. Given that several common medications used in older people contain anticholinergic properties, these findings highlight the care that should be made when considering the addition of a new medication in people with dementia. In particular, medications with anticholinergic properties should be carefully assessed

for their risk versus benefit. Where possible, alternative medications with lower or no anticholinergic properties should be used instead. Additionally, medications used in people with dementia should be regularly reviewed to reduce anticholinergic burden where possible.[33]

This study has several strengths and limitations. Strengths lie in the large, nationally representative cohort of individuals with dementia. Additionally, a wider range of dementia disorder subtypes were included compared with other studies, and we were able to make comparisons across different disorders. The ascertainment of medical diagnoses and medications employed the use of national registers that were complete and allowed for follow-up of individuals, thus eliminating any potential attrition or recall bias. Our medication exposure was time-dependent, taking into account the change in prescribing patterns that occur after dementia diagnosis and thus more accurately reflective of medication use at the time of event. We also supplemented this analysis using baseline medication exposure, to investigate long-term effects of anticholinergic burden. Although we know that medications were dispensed and collected from pharmacies, we did not explore the impact of medication adherence. Additionally, we did not consider non-prescription medications such as those obtained over-the-counter, nor medications used infrequently, thus we may have underestimated the effects. We cannot exclude the possibility of bias due to unmeasured confounding, in particular confounding by indication. Although we adjusted for a range of important covariates, it was not possible to control for all factors that may influence a physician's decision to prescribe anticholinergic medications.

Conclusion

Our study found that total anticholinergic burden was associated with an increased risk of all-cause mortality and incident stroke in people with dementia. A dose-response relationship was

observed. This association remained significant in those with AD, mixed dementia and vascular dementia after stratifying by dementia disorder. Careful consideration should be made when prescribing medications with anticholinergic properties to people with dementia.

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Conflict of Interest

The authors have no conflict of interest to report

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Table 1. Baseline characteristics according to ACB score

	Total *N = 39107*	**0** *N = 24573*	**1** *N = 8239*	**≥2** *N = 6295*	**p-value**
Female, n (%)	23735 (60.7)	15013 (61.1)	4955 (60.1)	3767 (59.8)	0.098
MMSE, mean (SD)	20.43 (6.03)	20.47 (6.01)	20.41 (5.98)	20.29 (6.16)	0.08
Age, mean (SD)	79.92 (7.90)	79.38 (8.14)	80.73 (7.35)	80.95 (7.45)	<0.001
Residency, n (%)					
At home with coresident	16617 (42.5)	10694 (43.5)	3350 (40.7)	2573 (40.9)	<0.001
At home alone	18976 (48.5)	11821 (48.1)	4129 (50.1)	3026 (48.1)	
Institutionalized	3514 (9.0)	2058 (8.4)	760 (9.2)	696 (11.1)	
Home care, n (%)	12076 (30.9)	7233 (29.4)	2593 (31.5)	2250 (35.7)	<0.001
Dementia disorder, n (%)					
AD	13269 (33.9)	9279 (37.8)	2462 (29.9)	1528 (24.3)	<0.001
Mixed dementia	7235 (20.7)	4262 (17.3)	1667 (20.2)	1306 (20.7)	
Vascular dementia	5967 (15.3)	3196 (13.0)	1474 (17.9)	1297 (20.6)	
Dementia with Lewy bodies	879 (2.2)	577 (2.3)	156 (1.9)	146 (2.3)	
Frontotemporal dementia	639 (1.6)	454 (1.8)	112 (1.4)	73 (1.2)	
Parkinson's disease dementia	601 (1.5)	351 (1.4)	90 (1.1)	160 (2.5)	
Unspecified	9531 (24.4)	5816 (23.7)	2089 (25.4)	1626 (25.8)	
Other	986 (2.5)	638 (2.6)	189 (2.3)	159 (2.5)	
Charlson Comorbidity Index, mean (SD)	2.12 (1.63)	1.88 (1.45)	2.34 (1.70)	2.75 (1.96)	<0.001
Acute myocardial infarction	3948 (10.1)	1436 (5.8)	1241 (15.1)	1271 (20.2)	<0.001
Ischemic heart disease	7389 (18.9)	2758 (11.2)	2308 (28.0)	2323 (36.9)	<0.001
Atrial fibrillation	5800 (14.8)	1949 (7.9)	1671 (20.3)	2180 (34.6)	<0.001
Heart failure	3962 (10.1)	1289 (5.2)	1076 (13.1)	1597 (25.4)	<0.001
Diabetes	4957 (12.7)	2369 (9.6)	1327 (16.1)	1261 (20.0)	<0.001
Total number of drugs, mean, (SD)	6.53 (5.03)	4.61 (3.85)	8.52 (4.46)	11.41 (5.48)	<0.001
Use of any antidementia drugs, n (%)	19072 (48.8)	12672 (51.6)	3776 (45.8)	2624 (41.7)	<0.001

MMSE: Mini-mental state examination, AD: Alzheimer's disease

Table 2. Event rates for composite outcome, death, stroke and ischemic stroke by baseline ACB score

	Total *N = 39107*	**0** *N = 24573*	**1** *N = 8239*	**≥2** *N = 6295*	**p-value**
Composite outcome[a], n (%)	11224 (28.7)	6607 (26.9)	2466 (29.9)	2151 (34.2)	<0.001
PY follow up	92646.40	59757.56	19015.07	13873.77	
Composite outcome/1000 PY	121.1	110.6	129.7	155.0	
Deaths, n (%)	10357 (26.5)	6091 (24.8)	2294 (27.8)	1972 (31.3)	<0.001
PY follow up	94908.81	61087.21	19478.26	14343.34	
Deaths/1000 PY	109	100.0	117.8	137.5	
Strokes, n (%)	1904 (4.9)	1071 (4.4)	419 (5.1)	414 (6.6)	<0.001
PY follow up	92646.40	59757.56	19015.07	13873.77	
Strokes/ 1000 PY	20.6	17.9	22.0	29.8	
Ischemic strokes, n(%)	1461 (3.7)	804 (3.3)	335 (4.1)	322 (5.1)	<0.001
PY follow up	93118.28	60045.94	19105.77	13966.57	
Ischemic strokes/1000 PY	15.7	13.4	17.5	23.1	

PY: person-years

a. Composite of death or any stroke

Table 3. Hazard ratios for the association between time-varying ACB score and stroke and death in people with dementia (N=39,107)

	Composite stroke and death	Death	Stroke	Ischemic stroke
HRs (95% CI)[a]				
Continuous	1.05 (1.03 – 1.06)***	1.04 (1.02 – 1.06)***	1.11 (1.07 – 1.15)***	1.06 (1.02 – 1.11)**
Categorical				
0 (n=22919)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1 (n=9184)	1.09 (1.04 – 1.14)**	1.09 (1.04 – 1.14)**	0.97 (0.86 – 1.08)	1.01 (0.89 – 1.15)
≥2 (n=7004)	1.20 (1.14 – 1.26)***	1.18 (1.12 – 1.24)***	1.13 (1.00 – 1.27)*	1.15 (1.00 – 1.31)*

a. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

b. Subdistribution hazard ratio

*p <0.05

**p<0.01

***p<0.001

Table 4. Association between time-varying ACB scores and composite of stroke and death by dementia disorder (N=39,107)

	AD N = 13269	MixedD N = 7235	VaD N = 5967	DLB N = 879	FTD N = 639	PDD N = 601	Unspecified N = 9531	Other N = 986
HRs (95% CI)[a]								
Continuous	1.08 (1.05 – 1.12)***	1.05 (1.01 – 1.09)**	1.04 (1.01 – 1.08)*	0.94 (0.86 – 1.03)	0.95 (0.85 – 1.07)	0.94 (0.86 – 1.03)	1.06 (1.02 – 1.09)***	1.04 (0.95 – 1.14)
Categorical								
0 (n=22919)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1 (n=9184)	1.12 (1.02 – 1.22)*	1.04 (0.95 – 1.15)	1.10 (0.98 – 1.22)	1.04 (0.79 – 1.37)	1.04 (0.71 – 1.53)	0.53 (0.34 – 0.83)**	1.18 (1.08 – 1.30)***	0.97 (0.71 – 1.33)
≥2 (n=7004)	1.27 (1.15 – 1.40)***	1.17 (1.06 – 1.30)**	1.20 (1.08 – 1.34)**	0.83 (0.62 – 1.10)	0.88 (0.57 – 1.37)	0.82 (0.60 – 1.13)	1.30 (1.18 – 1.43)***	1.06 (0.78 – 1.45)

AD, Alzhiemer's disease; MixedD, mixed dementia; VaD, vascular dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PDD, Parkinson's disease dementia; HR, hazard ratio; CI, confidence interval

a. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

b. Additionally adjusted for dementia disorder

*p <0.05

**p<0.01

***p<0.001

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Anticholinergic Cognitive Burden scale drug scoring

Score 1	Score 2	Score 3
Alimemazine	Amantadine	Amitriptyline
Alverine	Belladonna	Amoxapine
Alprazolam	Carbamazepine	Atropine
Aripiprazole	Cyclobenzaprine	Benztropine
Atenolol	Cyproheptadine	Brompheniramine
Bupropion	Loxapine	Carbinoxamine
Captopril	Meperidine	Chlorpheniramine
Chlorthalidone	Methotrimeprazine	Chlorpromazine
Cimetidine	Molindone	Clemastine
Clidinium	Nefopam	Clomipramine
Clorazepate	Oxcarbazepine	Clozapine
Codeine	Pimozide	Darifenacin
Colchicine		Desipramine
Desloratadine		Dicyclomine
Diazepam		Dimenhydrinate
Digoxin		Diphenhydramine
Dipyridamole		Doxepin
Disopyramide		Fesoterodine

Score 1	Score 2	Score 3
Fentanyl		Flavoxate
Furosemide		Hydroxyzine
Fluvoxamine		Hyoscyamine
Haloperidol		Imipramine
Hydralazine		Meclizine
Hydrocortisone		Methocarbamol
Iloperidone		Nortriptyline
Isosorbide		Olanzapine
Levocetirizine		Orphenadrine
Loperamide		Oxybutynin
Loratadine		Paroxetine
Metoprolol		Perphenazine
Morphine		Promethazine
Nifedipine		Propantheline
Paliperidone		Propeverine
Prednisone		Quetiapine
Quinidine		Scopolamine
Ranitidine		Solifenacin
Risperidone		Thioridazine
Theophylline		Tolterodine

Score 1	Score 2	Score 3
Trazodone		Trifluoperazine
Triamterene		Trihexyphenidyl
Venlafaxine		Trimipramine
Warfarin		Trospium

Adapted from: Aging Brain Care. Anticholinergic Cognitive Burden Scale—2012 Update. Available: www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf. (Accessed February 7 2018)

Supplementary Table 2. Hazard ratios for the association between baseline ACB score and stroke and death in people with dementia

	Composite stroke and death	Death	Stroke	Ischemic stroke
HRs[a]				
Continuous	1.02 (1.01 – 1.04)**	1.01 (1.00 – 1.03)	1.08 (1.05 – 1.12)***	1.09 (1.05 – 1.13)***
Categorical				
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.03 (0.99 – 1.08)	1.04 (0.99 – 1.09)	1.09 (0.97 – 1.22)	1.14 (1.00 – 1.30)*
≥2	1.11 (1.11 – 1.16)***	1.08 (1.02 – 1.13)**	1.36 (1.21 – 1.53)***	1.37 (1.20 – 1.56)***

c. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

d. Subdistribution hazard ratio

*p <0.05

**p<0.01

***p<0.001

Supplementary Table 3. Association between baseline ACB scores and composite of stroke and death by dementia disorder

	AD N = 13269	MixedD N = 7235	VaD N = 5967	DLB N = 879	FTD N = 639	PDD N = 601	Unspecified N = 9531	Other N = 986
HRs[a]								
Continuous	1.03 (0.99 – 1.06)	1.02 (0.98 – 1.05)	1.02 (0.99 – 1.06)	0.95 (0.87 – 1.04)	1.04 (0.93 – 1.17)	1.03 (0.95 – 1.11)	1.03 (1.00 – 1.06)	1.10 (1.00 – 1.21)*
Categorical								
0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	1.09 (1.00 – 1.19)	0.92 (0.78 – 1.02)	1.08 (0.97 – 1.21)	1.11 (0.84 – 1.46)	1.19 (0.80 – 1.78)	0.80 (0.53 – 1.20)	1.05 (0.95 – 1.15)	0.97 (0.71 – 1.34)
≥2	1.11 (1.00 – 1.23)*	1.08 (0.97 – 1.20)	1.06 (0.95 – 1.19)	0.83 (0.62 – 1.11)	1.44 (0.92 – 2.26)	1.02 (0.75 – 1.39)	1.21 (1.09 – 1.33)***	1.17 (0.84 – 1.63)

AD, Alzhiemer's disease; MixedD, mixed dementia; VaD, vascular dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PDD, Parkinson's disease dementia; HR, hazard ratio; CI, confidence interval

c. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

d. Additionally adjusted for dementia disorder

*p <0.05

**p<0.01

***p<0.001